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I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

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Signed Andrew Cerny

Dated 20 January 2000

Patents Form 1/77
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Office

1/77

# quest for grant of a patent

*(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)*





The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference

JRM/TAB/PHM.98-155/GB/P

2. Patent application number
*(The Patent Office will fill in this part)*

9900334.5

7 JAN 1999

3. Full name, address and nationality of each applicant *(underline all surnames)*

Angiogene Pharmaceuticals Ltd.
14 Plowden Park, Aston Rowant,
Watlington, Oxfordshire OX9 5SX

(WATLINGTON)

Patents ADP number *(if you know it)*

7246475001

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

Tricylic Vascular Damaging Agents

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

ASTRAZENECA
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(WATLINGTON)

F51/77

Patents ADP number *(if you know it)*

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

| Country | Priority application number *(if you know it)* | Date of filing *(day / month / year)* |
|---|---|---|

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

| Number of earlier application | Date of filing *(day / month / year)* |
|---|---|

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

*a) any applicant named in part 3 is not an inventor, or*

*b) there is an inventor who is not named as an applicant, or*

*c) any named applicant is a corporate body.*
*See note (d))*

**Patents Form 1/77**

1. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form

Description 36

Claim(s)

Abstract

Drawing(s)



10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*

Request for preliminary examination and search *(Patents Form 9/77)*

Request for substantive examination *(Patents Form 10/77)*

Any other documents *(please specify)*

11. I/We request the grant of a patent on the basis of this application.

Signature Date 18 Dec 1998

12. Name and daytime telephone number of person to contact in the United Kingdom Dr Peter DAVIS
01844 354562

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***After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.***

**Notes**

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*d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.*

*e) Once you have filled in the form you must remember to sign and date it.*

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# TRICYCLIC VASCULAR DAMAGING AGENTS

The present invention relates to vascular damaging agents, in particular to the use of compounds of the invention in the manufacture of medicaments for use in the production of antiangiogenic effects in warm-blooded animals such as humans, to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds as active ingredient, to methods for the treatment of disease states associated with angiogenesis and to the use of such compounds as medicaments.

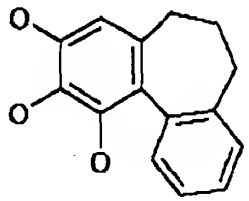
Normal angiogenesis plays an important role in a variety of processes including embryonic development, wound healing and several components of female reproductive function. Undesirable or pathological angiogenesis has been associated with disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995, Trends Pharmacol. Sci. 16: 57-66; Folkman, 1995, Nature Medicine 1: 27-31). Formation of new vasculature by angiogenesis is a key pathological feature of several diseases (J. Folkman, New England Journal of Medicine 333, 1757-1763 (1995)). For example, for a solid tumour to grow it must develop its own blood supply upon which it depends critically for the provision of oxygen and nutrients; if this blood supply is mechanically shut off the tumour undergoes necrotic death. Neovascularisation is also a clinical feature of skin lesions in psoriasis, of the invasive pannus in the joints of rheumatoid arthritis patients and of atherosclerotic plaques. Retinal neovascularisation is pathological in macular degeneration and in diabetic retinopathy.

Reversal of neovascularisation by damaging the newly-formed vascular endothelium is expected to have a beneficial therapeutic effect. The present invention is based on the discovery of tricyclic compounds that surprisingly specifically damage newly formed vasculature without affecting the normal, established vascular endothelium of the host species, a property of value in the treatment of disease states associated with angiogenesis such as cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation.

Compounds of the present invention are colchinol derivatives. Colchinol derivatives for example *N*-acetyl-colchinol are known. Anti-tumour effects have been noted on animal

models (see for example - Jnl. Natl. Cancer Inst. 1952, 13, 379-392). However, the effect studied was that of gross damage (haemorrhage, softening and necrosis) and there is no suggestion of treatment of inappropriate angiogenesis by destruction of neovasculature.

A search of Chemical Abstracts (post 1955) based on the substructure:

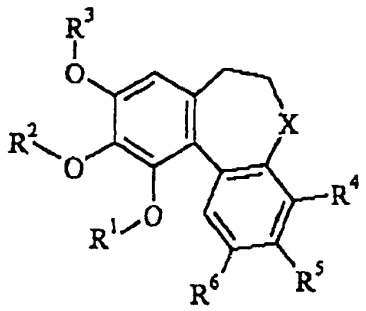


revealed a number of colchinol related structures. To the extent that any of these compounds have been studied for anti-cancer activity it is because tubulin-binding agents like colchinol might be expected to be anti-mitotic and therefore to have a direct effect on tumour cells. Some compounds which bind tubulin have been shown to have anti-vascular effects when given at their maximum tolerated dose (MTD) (S.A. Hill et al. Eur. J Cancer, 29A, 1320-1324 (1993)) but other tubulin-binding agents have no vascular-damaging activity even when administered at the MTD, for example docetaxel (Lancet, 1994, 344, 1267-1271). In the course of the work on the present invention, the issue of the relevance of tubulin-binding properties to possible effectiveness as anti-vascular agent was studied but no predictability was found. Certain compounds structurally related to those of the present invention but not of the present invention, have been found to have a therapeutic window (ratio of MTD to minimum effective dose (MED)) too small for potential clinical effectiveness.

The presence of tubulin-binding properties is then not predictive for antivascular activity. Compounds which have strong tubulin-binding activity give rise to antimitotic effects *in vivo*. The effects of this are most noticeable on proliferating tissue and give rise to undesirable effects, for example on the proliferative tissue of the gut and bone marrow. Compounds which have vascular damaging activity but weak tubulin-binding activity would therefore be useful in the treatment of diseases involving angiogenesis.

It is believed, though this is not limiting on the invention, that the use of compounds of the invention damages newly-formed vasculature, for example the vasculature of tumours, thus effectively reversing the process of angiogenesis as compared to known anti-angiogenic agents which tend to be less effective once the vasculature has formed.

According to one aspect of the present invention there is provided the use of a compound of the formula I:



(I)

wherein

X is

-C(O)-, -C(S)-, -C=NOH, or -CH($R^7$)- wherein $R^7$ is hydrogen, hydroxy, $C_{1-7}$alkoxy or -$NR^8R^9$ (wherein $R^8$ is a group -$Y^1R^{10}$ (wherein $Y^1$ is a direct bond, -C(O)-, -C(S)-, -S-, -C(O)O-, -C(O)$NR^{11}$-, -$SO_2$- or -$SO_2NR^{12}$- (wherein $R^{11}$ and $R^{12}$, which may be the same or different, each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{10}$ is selected from one of the following four groups:

1) hydrogen, $C_{1-7}$alkyl or $C_{3-7}$cycloalkyl

(which alkyl or cycloalkyl group may bear one or more substituents selected from: halogeno, amino, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, hydroxy, $C_{1-4}$alkoxy, $C_{1-4}$alkylsulphanyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonylamino, $C_{1-4}$alkanoyl, phenyl, nitro, sulphate, phosphate and a group -$Y^2R^{13}$ (wherein $Y^2$ is -$NR^{14}$C(O)- or -O-C(O)- (wherein $R^{14}$ represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{13}$ is $C_{1-7}$alkyl, $C_{3-7}$cycloalkyl or a group $R^{15}$ wherein $R^{15}$ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, cyano, -$CONR^{16}R^{17}$ and -$NR^{18}COR^{19}$ (wherein $R^{16}$, $R^{17}$, $R^{18}$ and $R^{19}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl)));

2) $R^{15}$ wherein $R^{15}$ is as defined hereinbefore;

3) $C_{2-7}$alkenyl$R^{15}$ (wherein $R^{15}$ is as defined hereinbefore); and

4) $C_{3-7}$alkynyl$R^{15}$ (wherein $R^{15}$ is as defined hereinbefore));

and $R^9$ is hydrogen, $C_{1-7}$alkyl or $C_{3-7}$cycloalkyl, which alkyl or cycloalkyl group may bear one or more substituents selected from $C_{1-4}$alkoxy and phenyl);

$R^1$, $R^2$ and $R^3$ are each independently

hydrogen, $PO_3H_2$, sulphate, $C_{3-7}$cycloalkyl, $C_{2-7}$alkenyl, $C_{2-7}$alkynyl, $C_{1-7}$alkanoyl, a group $R^{20}C_{1-7}$alkyl (wherein $R^{20}$ is phenyl which may bear one or more substituents selected from $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$aminoalkyl and $C_{1-4}$hydroxyalkoxy), $C_{1-7}$alkyl or $C_{1-7}$alkylsulphonyl (which alkyl or alkylsulphonyl group may bear one or more substituents selected from: halogeno, amino, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, hydroxy, $C_{1-4}$alkoxy, $C_{1-4}$alkylsulphanyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonylamino, $C_{1-4}$alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group $-Y^2R^{21}$ (wherein $Y^2$ is $-NR^{22}C(O)-$ or $-O-C(O)-$ (wherein $R^{22}$ represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{21}$ is $C_{1-7}$alkyl, $C_{3-7}$cycloalkyl or a group $R^{23}$ wherein $R^{23}$ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, cyano, $-CONR^{24}R^{25}$ and $-NR^{26}COR^{27}$ (wherein $R^{24}$, $R^{25}$, $R^{26}$ and $R^{27}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl)));

with the proviso that at least two of $R^1$, $R^2$ and $R^3$ are $C_{1-7}$alkyl;

$R^4$, $R^5$ and $R^6$ are each independently selected from:

hydrogen, $-OPO_3H_2$, cyano, halogeno, nitro, amino, carboxy, hydroxy, $C_{1-7}$alkoxy, $C_{1-7}$alkanoyl, $C_{1-7}$thioalkoxy, $C_{1-7}$alkyl,

(which alkyl group may bear one or more substituents selected from: halogeno, amino, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, hydroxy, $C_{1-4}$alkoxy, $C_{1-4}$alkylsulphanyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonylamino, $C_{1-4}$alkanoyl, carboxy, phenyl, sulphate, phosphate and a group $-Y^3R^{28}$ (wherein $Y^3$ is $-NR^{29}C(O)-$ or $-O-C(O)-$

(wherein $R^{29}$ represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{28}$ is $C_{1-7}$alkyl, $C_{3-7}$cycloalkyl or a group $R^{30}$ wherein $R^{30}$ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, cyano, $-CONR^{31}R^{32}$ and $-NR^{31}COR^{32}$ (wherein $R^{31}$, $R^{32}$, $R^{33}$ and $R^{34}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl))), and

a group $-Y^4R^{35}$

(wherein $Y^4$ is -C(O)-, -OC(O)-, -O-, -SO-, $-SO_2-$, $-OSO_2-$, $-NR^{36}-$, $-NR^{37}C(O)-$, -OC(O)O-, $-C(O)NR^{38}-$ or $-NR^{39}C(O)O-$ (wherein $R^{36}$, $R^{37}$, $R^{38}$ and $R^{39}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{35}$ is

a sugar moiety, a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, sulphate, $C_{1-7}$alkyl, $C_{1-7}$alkoxy, $C_{1-7}$alkanoyl, amino$C_{1-7}$alkylamino, $C_{1-7}$alkylamino$C_{1-7}$alkylamino, di($C_{1-7}$alkyl)amino$C_{1-7}$alkylamino, $C_{1-7}$alkylphosphate

(which alkyl, alkoxy, alkanoyl, aminoalkylamino, alkylaminoalkylamino, dialkylaminoalkylamino, or alkylphosphate may bear one or more substituents selected from:

halogeno, amino, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, hydroxy, $C_{1-4}$alkoxy, $C_{1-4}$alkylsulphanyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonylamino, $C_{1-4}$alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group $-Y^5R^{40}$ (wherein $Y^5$ is $-NR^{41}C(O)-$, $-C(O)NR^{42}-$, -C(O)-O- or -O-C(O)- (wherein $R^{41}$ and $R^{42}$ which may be the same or different each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{40}$ is $C_{1-7}$alkyl, $C_{3-7}$cycloalkyl, carboxy$C_{1-7}$alkyl or a group $R^{43}$ wherein $R^{43}$ is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, cyano, $-CONR^{44}R^{45}$ and $-NR^{46}COR^{47}$ (wherein $R^{44}$, $R^{45}$, $R^{46}$ and $R^{47}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl))),

$R^{48}$ (wherein $R^{48}$ is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, phenyl, cyano, $-CONR^{49}R^{50}$ and $-NR^{51}COR^{52}$ (wherein $R^{49}$, $R^{50}$, $R^{51}$ and $R^{52}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl)), or

$R^{53}$ (wherein $R^{53}$ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, $C_{1-4}$alkyl, $C_{1-4}$hydroxyalkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxy$C_{1-4}$alkyl, $C_{1-4}$alkylsulphonyl$C_{1-4}$alkyl and $R^{54}$ (wherein $R^{54}$ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, $C_{1-4}$alkyl, $C_{1-4}$hydroxyalkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxy$C_{1-4}$alkyl and $C_{1-4}$alkylsulphonyl$C_{1-4}$alkyl)));

with the proviso that $R^5$ is not hydroxy, alkoxy, substituted alkoxy, $-OPO_3H_2$, $-O-C_{1-7}$alkanoyl or benzyloxy;

and salts thereof, pharmaceutically acceptable salts thereof, solvates and hydrates thereof, and prodrugs thereof for example esters, amides and sulphides, in the manufacture of a medicament for use in the production of a vascular damaging effect in warm-blooded animals such as humans.

According to a further aspect of the present invention there is provided the use of a compound of the formula I as defined hereinbefore and salts thereof, pharmaceutically acceptable salts thereof, solvates and hydrates thereof, and prodrugs thereof for example esters, amides and sulphides, in the manufacture of a medicament for use in the production of a vascular damaging effect at less than the maximum tolerated dose in warm-blooded animals such as humans.

Conveniently X is -C(O)-, -C(S)-, or $-CH(R^7)-$ wherein $R^7$ is hydrogen, hydroxy or $-NR^8R^9$ (wherein $R^8$ is a group $-Y^1R^{10}$ (wherein $Y^1$ is a direct bond, -C(O)-, -C(S)-, -C(O)O-, $-C(O)NR^{11}-$, $-SO_2-$ or $-SO_2NR^{12}-$ (wherein $R^{11}$ and $R^{12}$, which may be the same or different,

each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{10}$ is selected from one of the following two groups:

1) hydrogen, $C_{1-7}$alkyl or $C_{3-7}$cycloalkyl

(which alkyl or cycloalkyl group may bear one or more substituents selected from: halogeno, amino, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, hydroxy, $C_{1-4}$alkoxy, $C_{1-4}$alkylsulphanyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonylamino, $C_{1-4}$alkanoyl, phenyl, nitro, sulphate, phosphate and a group $-Y^2R^{13}$ (wherein $Y^2$ is $-NR^{14}C(O)-$ or $-O-C(O)-$ (wherein $R^{14}$ represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{13}$ is $C_{1-7}$alkyl, $C_{3-7}$cycloalkyl or a group $R^{15}$ wherein $R^{15}$ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, cyano, $-CONR^{16}R^{17}$ and $-NR^{18}COR^{19}$ (wherein $R^{16}$, $R^{17}$, $R^{18}$ and $R^{19}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl)));

2) $R^{15}$ wherein $R^{15}$ is as defined hereinbefore;

and $R^9$ is hydrogen, $C_{1-7}$alkyl or $C_{3-7}$cycloalkyl, which alkyl or cycloalkyl group may bear one or more substituents selected from $C_{1-4}$alkoxy and phenyl).

Preferably X is $-C(O)-$, $-CH_2-$, $-CH(OH)-$ or $-CH(NHC(O)CH_3)-$.

More preferably X is $-CH(NHC(O)CH_3)-$.

Conveniently $R^1$, $R^2$ and $R^3$ are each independently hydrogen, $PO_3H_2$, sulphate, $C_{1-7}$alkyl, $C_{3-7}$cycloalkyl, $C_{2-7}$alkenyl, $C_{2-7}$alkynyl, $C_{1-7}$alkanoyl, $C_{1-7}$alkylsulphonyl or a group $R^{20}C_{1-7}$alkyl (wherein $R^{20}$ is phenyl which may bear one or more substituents selected from $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$aminoalkyl and $C_{1-4}$hydroxyalkoxy);

with the proviso that at least two of $R^1$, $R^2$ and $R^3$ are $C_{1-7}$alkyl.

Preferably $R^1$, $R^2$ and $R^3$ are each independently $C_{1-4}$alkyl.

More preferably $R^1$, $R^2$ and $R^3$ are each methyl.

Conveniently $R^4$ is

hydrogen, cyano, halogeno, nitro, amino, hydroxy, $C_{1-7}$alkoxy, $C_{1-7}$thioalkoxy, $C_{1-7}$alkanoyl or $C_{1-7}$alkyl,

(which alkyl group may bear one or more substituents selected from

halogeno, amino, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, hydroxy, $C_{1-4}$alkoxy, $C_{1-4}$alkylsulphanyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonylamino, $C_{1-4}$alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group $-Y^3R^{28}$ (wherein $Y^3$ is $-NR^{29}C(O)-$ or $-O-C(O)-$ (wherein $R^{29}$ represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{28}$ is $C_{1-7}$alkyl, $C_{3-7}$cycloalkyl or a group $R^{30}$ wherein $R^{30}$ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, cyano, $-CONR^{31}R^{32}$ and $-NR^{31}COR^{32}$ (wherein $R^{31}$, $R^{32}$, $R^{33}$ and $R^{34}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl))).

Preferably $R^4$ is hydrogen, hydroxy, halogeno, cyano, amino or $C_{1-7}$alkanoyl.

More preferably $R^4$ is hydrogen.

Conveniently $R^5$ and $R^6$ are each independently selected from:

hydrogen, $-OPO_3H_2$, cyano, halogeno, nitro, amino, carboxy, hydroxy, $C_{1-7}$alkoxy, $C_{1-7}$alkanoyl, $C_{1-7}$thioalkoxy, $C_{1-7}$alkyl,

(which alkyl group may bear one or more substituents selected from:

halogeno, amino, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, hydroxy, $C_{1-4}$alkoxy, $C_{1-4}$alkylsulphanyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonylamino, $C_{1-4}$alkanoyl, carboxy, phenyl, sulphate, phosphate and a group $-Y^3R^{28}$ (wherein $Y^3$ is $-NR^{29}C(O)-$ or $-O-C(O)-$ (wherein $R^{29}$ represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{28}$ is $C_{1-7}$alkyl, $C_{3-7}$cycloalkyl or a group $R^{30}$ wherein $R^{30}$ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, cyano, $-CONR^{31}R^{32}$ and $-NR^{31}COR^{32}$ (wherein $R^{31}$, $R^{32}$, $R^{33}$ and $R^{34}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl))), and

a group $-Y^4R^{35}$

(wherein $Y^4$ is -C(O)-, -OC(O)-, -O-, -SO-, $-SO_2-$, $-OSO_2-$, $-NR^{36}-$, $-NR^{37}C(O)-$, $-OC(O)O-$, $-C(O)NR^{38}-$ or $-NR^{39}C(O)O-$ (wherein $R^{36}$, $R^{37}$, $R^{38}$ and $R^{39}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{35}$ is a sugar moiety, a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, sulphate, $C_{1-7}$alkyl, $C_{1-7}$alkoxy, $C_{1-7}$alkanoyl, amino$C_{1-7}$alkylamino, $C_{1-7}$alkylamino$C_{1-7}$alkylamino, di($C_{1-7}$alkyl)amino$C_{1-7}$alkylamino, $C_{1-7}$alkylphosphate

(which alkyl, alkoxy, alkanoyl, aminoalkylamino, alkylaminoalkylamino, dialkylaminoalkylamino, or alkylphosphate may bear one or more substituents selected from:

halogeno, amino, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, hydroxy, $C_{1-4}$alkoxy, $C_{1-4}$alkylsulphanyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonylamino, $C_{1-4}$alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group $-Y^5R^{40}$ (wherein $Y^5$ is $-NR^{41}C(O)-$, $-C(O)NR^{42}-$, -C(O)-O- or -O-C(O)- (wherein $R^{41}$ and $R^{42}$ which may be the same or different each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{40}$ is $C_{1-7}$alkyl, $C_{3-7}$cycloalkyl, carboxy$C_{1-7}$alkyl or a group $R^{43}$ wherein $R^{43}$ is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, cyano, $-CONR^{44}R^{45}$ and $-NR^{46}COR^{47}$ (wherein $R^{44}$, $R^{45}$, $R^{46}$ and $R^{47}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl))),

$R^{48}$ (wherein $R^{48}$ is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, phenyl, cyano, $-CONR^{49}R^{50}$ and $-NR^{51}COR^{52}$ (wherein $R^{49}$, $R^{50}$, $R^{51}$ and $R^{52}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl)), or

$R^{53}$ (wherein $R^{53}$ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which

heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, $C_{1-4}$alkyl, $C_{1-4}$hydroxyalkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxy$C_{1-4}$alkyl, $C_{1-4}$alkylsulphonyl$C_{1-4}$alkyl and $R^{54}$ (wherein $R^{54}$ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, $C_{1-4}$alkyl, $C_{1-4}$hydroxyalkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxy$C_{1-4}$alkyl and $C_{1-4}$alkylsulphonyl$C_{1-4}$alkyl)));

with the proviso that $R^5$ is not hydroxy, alkoxy, substituted alkoxy, $-OPO_3H_2$, $-O-C_{1-7}$alkanoyl or benzyloxy.

Preferably $R^6$ is hydrogen, halogeno, amino, carboxy, hydroxy, $C_{1-7}$alkoxy or a group $Y^4R^{35}$ (wherein $Y^4$ is -C(O)-, -O- or $-OSO_2-$ and $R^{35}$ is $C_{1-7}$alkyl, $C_{1-7}$alkoxy (which alkyl or alkoxy may bear one or more substituents selected from halogeno), $R^{48}$ (wherein $R^{48}$ is a benzyl group) or $R^{53}$ (wherein $R^{53}$ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms selected independently from O, S and N.

Preferably $R^6$ is hydrogen.

Preferably $R^5$ is hydrogen, halogeno, amino, carboxy, $C_{1-7}$alkanoyl, $C_{1-7}$thioalkoxy, or a group $-Y^4R^{35}$

(wherein $Y^4$ is -C(O)-, -OC(O)-, -O-, -SO-, $-OSO_2-$, $-NR^{36}-$, $-NR^{37}C(O)-$ or $-C(O)NR^{38}-$ (wherein $R^{36}$, $R^{37}$ and $R^{38}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{35}$ is

a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, $C_{1-7}$alkyl, $C_{1-7}$alkoxy, $C_{1-7}$alkanoyl,

(which alkyl, alkoxy or alkanoyl may bear one or more substituents selected from: halogeno, amino, hydroxy, and a group $-Y^5R^{40}$ (wherein $Y^5$ is -C(O)-O- or -O-C(O)- and $R^{40}$ is $C_{1-7}$alkyl or a group $R^{43}$ wherein $R^{43}$ is a benzyl group)),

$R^{48}$ (wherein $R^{48}$ is a phenyl group or a benzyl group which phenyl or benzyl group may bear one or more substituents selected from $C_{1-7}$alkyl), or

$R^{53}$ (wherein $R^{53}$ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, $C_{1-4}$alkyl, $C_{1-4}$hydroxyalkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxy$C_{1-4}$alkyl, $C_{1-4}$alkylsulphonyl$C_{1-4}$alkyl and $R^{54}$ (wherein $R^{54}$ is a 5-6-membered saturated heterocyclic group (linked via carbon or

nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from $C_{1-4}$alkyl));

with the proviso that $R^5$ is not -O-$C_{1-7}$alkanoyl or benzyloxy.

Preferred values for $R^5$ include alanylamino, *N*-(benzyloxycarbonylalanyl)amino, and 4-(piperidino)piperidin-1-ylcarbonyloxy.

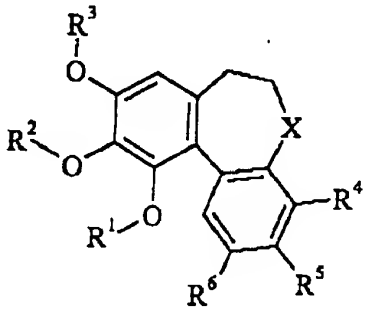
A more preferred value for $R^5$ is alanylamino.

Particular values of $R^5$ include amino $C_{1-7}$alkylamino and di$C_{1-7}$alkylamino, especially amino.

When $R^{35}$ is a sugar moiety it can be, for example a monosaccharide such as a glucuronyl, glucosyl or galactosyl group or a di- or trisaccharide.

When $R^{35}$ is a mono-, di-, tri- or tetra- peptide it is preferably derived from a natural alpha amino acid for example such as glycine, valine, lysine, alanine or serine.

According to another aspect of the present invention there is provided the use of a compound of the formula II:



(II)

wherein

X is

-C(O)-, -C(S)-, or -CH($R^7$)- wherein $R^7$ is hydrogen, hydroxy or -$NR^8R^9$ (wherein $R^8$ is a group -$Y^1R^{10}$ (wherein $Y^1$ is a direct bond, -C(O)-, -C(S)-, -C(O)O-, -C(O)$NR^{11}$-, -$SO_2$- or -$SO_2NR^{12}$- (wherein $R^{11}$ and $R^{12}$, which may be the same or different, each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{10}$ is selected from one of the following two groups:

1) hydrogen, $C_{1-7}$alkyl or $C_{3-7}$cycloalkyl

(which alkyl or cycloalkyl group may bear one or more substituents selected from: halogeno, amino, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, hydroxy, $C_{1-4}$alkoxy, $C_{1-4}$alkylsulphanyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonylamino, $C_{1-4}$alkanoyl, phenyl, nitro,

sulphate, phosphate and a group $-Y^2R^{13}$ (wherein $Y^2$ is $-NR^{14}C(O)-$ or $-O-C(O)-$ (wherein $R^{14}$ represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{13}$ is $C_{1-7}$alkyl, $C_{3-7}$cycloalkyl or a group $R^{15}$ wherein $R^{15}$ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, cyano, $-CONR^{16}R^{17}$ and $-NR^{18}COR^{19}$ (wherein $R^{16}$, $R^{17}$, $R^{18}$ and $R^{19}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl)));

2) $R^{15}$ wherein $R^{15}$ is as defined hereinbefore;

and $R^9$ is hydrogen, $C_{1-7}$alkyl or $C_{3-7}$cycloalkyl, which alkyl or cycloalkyl group may bear one or more substituents selected from $C_{1-4}$alkoxy and phenyl);

$R^1$, $R^2$ and $R^3$ are each independently

hydrogen, $PO_3H_2$, sulphate, $C_{3-7}$cycloalkyl, $C_{2-7}$alkenyl, $C_{2-7}$alkynyl, $C_{1-7}$alkanoyl, a group $R^{20}C_{1-7}$alkyl (wherein $R^{20}$ is phenyl which may bear one or more substituents selected from $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$aminoalkyl and $C_{1-4}$hydroxyalkoxy), $C_{1-7}$alkyl or $C_{1-7}$alkylsulphonyl (which alkyl or alkylsulphonyl group may bear one or more substituents selected from: halogeno, amino, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, hydroxy, $C_{1-4}$alkoxy, $C_{1-4}$alkylsulphanyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonylamino, $C_{1-4}$alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group $-Y^2R^{21}$ (wherein $Y^2$ is $-NR^{22}C(O)-$ or $-O-C(O)-$ (wherein $R^{22}$ represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{21}$ is $C_{1-7}$alkyl, $C_{3-7}$cycloalkyl or a group $R^{23}$ wherein $R^{23}$ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, cyano, $-CONR^{24}R^{25}$ and $-NR^{26}COR^{27}$ (wherein $R^{24}$, $R^{25}$, $R^{26}$ and $R^{27}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl)));

with the proviso that at least two of $R^1$, $R^2$ and $R^3$ are $C_{1-7}$alkyl;

$R^4$ is

hydrogen, cyano, halogeno, nitro, amino, hydroxy, $C_{1-7}$alkoxy, $C_{1-7}$thioalkoxy, $C_{1-7}$alkanoyl or $C_{1-7}$alkyl,

(which alkyl group may bear one or more substituents selected from: halogeno, amino, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, hydroxy, $C_{1-4}$alkoxy, $C_{1-4}$alkylsulphanyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonylamino, $C_{1-4}$alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group $-Y^3R^{28}$ (wherein $Y^3$ is $-NR^{29}C(O)-$ or $-O-C(O)-$ (wherein $R^{29}$ represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{28}$ is $C_{1-7}$alkyl, $C_{3-7}$cycloalkyl or a group $R^{30}$ wherein $R^{30}$ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, cyano, $-CONR^{31}R^{32}$ and $-NR^{31}COR^{32}$ (wherein $R^{31}$, $R^{32}$, $R^{33}$ and $R^{34}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl)));

$R^5$ and $R^6$ are each independently

hydrogen, $-OPO_3H_2$, cyano, halogeno, nitro, amino, carboxy, hydroxy, $C_{1-7}$alkoxy, $C_{1-7}$alkanoyl, $C_{1-7}$thioalkoxy, $C_{1-7}$alkyl,

(which alkyl group may bear one or more substituents selected from: halogeno, amino, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, hydroxy, $C_{1-4}$alkoxy, $C_{1-4}$alkylsulphanyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonylamino, $C_{1-4}$alkanoyl, carboxy, phenyl, sulphate, phosphate and a group $-Y^3R^{28}$ (wherein $Y^3$ is $-NR^{29}C(O)-$ or $-O-C(O)-$ (wherein $R^{29}$ represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{28}$ is $C_{1-7}$alkyl, $C_{3-7}$cycloalkyl or a group $R^{30}$ wherein $R^{30}$ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, cyano, $-CONR^{31}R^{32}$ and $-NR^{31}COR^{32}$ (wherein $R^{31}$, $R^{32}$, $R^{33}$ and $R^{34}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl))), and

a group $-Y^4R^{35}$

(wherein $Y^4$ is -C(O)-, -OC(O)-, -O-, -SO-, $-SO_2-$, $-OSO_2-$, $-NR^{36}-$, $-NR^{37}C(O)-$, -OC(O)O-, $-C(O)NR^{38}-$ or $-NR^{39}C(O)O-$ (wherein $R^{36}$, $R^{37}$, $R^{38}$ and $R^{39}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{35}$ is a sugar moiety, a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, sulphate, $C_{1-7}$alkyl, $C_{1-7}$alkoxy, $C_{1-7}$alkanoyl, amino$C_{1-7}$alkylamino, $C_{1-7}$alkylamino$C_{1-7}$alkylamino, di($C_{1-7}$alkyl)amino$C_{1-7}$alkylamino, $C_{1-7}$alkylphosphate

(which alkyl, alkoxy, alkanoyl, aminoalkylamino, alkylaminoalkylamino, dialkylaminoalkylamino, or alkylphosphate may bear one or more substituents selected from:

halogeno, amino, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, hydroxy, $C_{1-4}$alkoxy, $C_{1-4}$alkylsulphanyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonylamino, $C_{1-4}$alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group $-Y^5R^{40}$ (wherein $Y^5$ is $-NR^{41}C(O)-$, $-C(O)NR^{42}-$, -C(O)-O- or -O-C(O)- (wherein $R^{41}$ and $R^{42}$ which may be the same or different each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{40}$ is $C_{1-7}$alkyl, $C_{3-7}$cycloalkyl, carboxy$C_{1-7}$alkyl or a group $R^{43}$ wherein $R^{43}$ is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, cyano, $-CONR^{44}R^{45}$ and $-NR^{46}COR^{47}$ (wherein $R^{44}$, $R^{45}$, $R^{46}$ and $R^{47}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl))),

$R^{48}$ (wherein $R^{48}$ is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, phenyl, cyano, $-CONR^{49}R^{50}$ and $-NR^{51}COR^{52}$ (wherein $R^{49}$, $R^{50}$, $R^{51}$ and $R^{52}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl)), or

$R^{53}$ (wherein $R^{53}$ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which

heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, $C_{1-4}$alkyl, $C_{1-4}$hydroxyalkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxy$C_{1-4}$alkyl, $C_{1-4}$alkylsulphonyl$C_{1-4}$alkyl and $R^{54}$ (wherein $R^{54}$ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, $C_{1-4}$alkyl, $C_{1-4}$hydroxyalkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxy$C_{1-4}$alkyl and $C_{1-4}$alkylsulphonyl$C_{1-4}$alkyl)));

with the proviso that $R^5$ is not hydroxy, alkoxy, substituted alkoxy, $-OPO_3H_2$, -O-$C_{1-7}$alkanoyl or benzyloxy;

with the further proviso that at least one of $R^5$ or $R^6$ is a group $-Y^4R^{35}$ (wherein $Y^4$ and $R^{35}$ are as defined hereinbefore) but with the further provisos

that when $R^5$ is $-Y^4R^{35}$ and $R^6$ is hydrogen, hydroxy or methoxy $-Y^4R^{35}$ is not selected from cases wherein:

$Y^4$ is -C(O)-, -OC(O)-, -O-, -SO-, $-OSO_2$-, $-NR^{36}$-, $-NR^{37}C(O)$- or $-C(O)NR^{38}$- (wherein $R^{36}$, $R^{37}$ and $R^{38}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{35}$ is

a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, $C_{1-7}$alkyl, $C_{1-7}$alkoxy, $C_{1-7}$alkanoyl,

(which alkyl, alkoxy or alkanoyl may bear one or more substituents selected from: halogeno, hydroxy, and a group $-Y^5R^{40}$ (wherein $Y^5$ is -C(O)-O- or -O-C(O)- and $R^{40}$ is $C_{1-7}$alkyl)), or

$R^{48}$ (wherein $R^{48}$ is a phenyl group or a benzyl group which phenyl or benzyl group may bear one or more substituents selected from $C_{1-7}$alkyl); and

that when $R^6$ is $-Y^4R^{35}$ and $R^5$ is hydrogen, hydroxy or methoxy $-Y^4R^{35}$ is not selected from cases wherein:

$Y^4$ is -C(O)-, -O- or $-OSO_2$- and $R^{35}$ is

$C_{1-7}$alkyl, $C_{1-7}$alkoxy

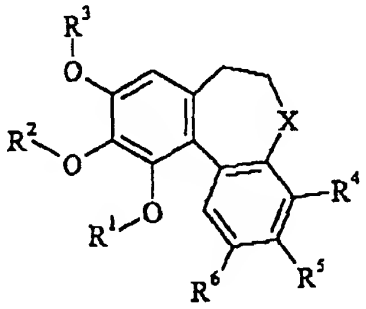
(which alkyl, alkoxy or alkanoyl may bear one or more substituents selected from: halogeno),

$R^{48}$ (wherein $R^{48}$ is a benzyl group which phenyl or benzyl group may bear one or more substituents selected from $C_{1-7}$alkyl), or

$R^{53}$ (wherein $R^{53}$ is piperidinyl);

and salts thereof, pharmaceutically acceptable salts thereof, solvates and hydrates thereof, and prodrugs thereof for example esters, amides and sulphides, in the manufacture of a medicament for use in the production of a vascular damaging effect in warm-blooded animals such as humans.

According to a further aspect of the present invention there is provided a compound of the formula III:



(III)

wherein

X is

-C(O)-, -C(S)-, or -CH($R^7$)- wherein $R^7$ is hydrogen, hydroxy or -$NR^8R^9$ (wherein $R^8$ is a group -$Y^1R^{10}$ (wherein $Y^1$ is a direct bond, -C(O)-, -C(S)-, -C(O)O-, -C(O)$NR^{11}$-, -$SO_2$- or -$SO_2NR^{12}$- (wherein $R^{11}$ and $R^{12}$, which may be the same or different, each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{10}$ is selected from one of the following two groups:

1) hydrogen, $C_{1-7}$alkyl or $C_{3-7}$cycloalkyl

(which alkyl or cycloalkyl group may bear one or more substituents selected from: halogeno, amino, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, hydroxy, $C_{1-4}$alkoxy, $C_{1-4}$alkylsulphanyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonylamino, $C_{1-4}$alkanoyl, phenyl, nitro, sulphate, phosphate and a group -$Y^2R^{13}$ (wherein $Y^2$ is -$NR^{14}$C(O)- or -O-C(O)- (wherein $R^{14}$ represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{13}$ is $C_{1-7}$alkyl, $C_{3-7}$cycloalkyl or a group $R^{15}$ wherein $R^{15}$ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-}$

$_4$hydroxyalkoxy, carboxy, cyano, -$CONR^{16}R^{17}$ and -$NR^{18}COR^{19}$ (wherein $R^{16}$, $R^{17}$, $R^{18}$ and $R^{19}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl)));

2) $R^{15}$ wherein $R^{15}$ is as defined hereinbefore;

and $R^9$ is hydrogen, $C_{1-7}$alkyl or $C_{3-7}$cycloalkyl, which alkyl or cycloalkyl group may bear one or more substituents selected from $C_{1-4}$alkoxy and phenyl);

$R^1$, $R^2$ and $R^3$ are each independently

hydrogen, $PO_3H_2$, sulphate, $C_{3-7}$cycloalkyl, $C_{2-7}$alkenyl, $C_{2-7}$alkynyl, $C_{1-7}$alkanoyl, a group $R^{20}C_{1-7}$alkyl (wherein $R^{20}$ is phenyl which may bear one or more substituents selected from $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$aminoalkyl and $C_{1-4}$hydroxyalkoxy), $C_{1-7}$alkyl or $C_{1-7}$alkylsulphonyl (which alkyl or alkylsulphonyl group may bear one or more substituents selected from: halogeno, amino, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, hydroxy, $C_{1-4}$alkoxy, $C_{1-4}$alkylsulphanyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonylamino, $C_{1-4}$alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group -$Y^2R^{21}$ (wherein $Y^2$ is -$NR^{22}C(O)$- or -O-C(O)- (wherein $R^{22}$ represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{21}$ is $C_{1-7}$alkyl, $C_{3-7}$cycloalkyl or a group $R^{23}$ wherein $R^{23}$ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, cyano, -$CONR^{24}R^{25}$ and -$NR^{26}COR^{27}$ (wherein $R^{24}$, $R^{25}$, $R^{26}$ and $R^{27}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl)));

with the proviso that at least two of $R^1$, $R^2$ and $R^3$ are $C_{1-7}$alkyl;

$R^4$ is

hydrogen, cyano, halogeno, nitro, amino, hydroxy, $C_{1-7}$alkoxy, $C_{1-7}$thioalkoxy, $C_{1-7}$alkanoyl or $C_{1-7}$alkyl,

(which alkyl group may bear one or more substituents selected from: halogeno, amino, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, hydroxy, $C_{1-4}$alkoxy, $C_{1-4}$alkylsulphanyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonylamino, $C_{1-4}$alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group -$Y^3R^{28}$ (wherein $Y^3$ is -$NR^{29}C(O)$- or -O-C(O)- (wherein $R^{29}$ represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{28}$ is $C_{1-}$

$_7$alkyl, $C_{3-7}$cycloalkyl or a group $R^{30}$ wherein $R^{30}$ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, cyano, $-CONR^{31}R^{32}$ and $-NR^{31}COR^{32}$ (wherein $R^{31}$, $R^{32}$, $R^{33}$ and $R^{34}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl)));

$R^5$ and $R^6$ are each independently

hydrogen, $-OPO_3H_2$, cyano, halogeno, nitro, amino, carboxy, hydroxy, $C_{1-7}$alkoxy, $C_{1-7}$alkanoyl, $C_{1-7}$thioalkoxy, $C_{1-7}$alkyl,

(which alkyl group may bear one or more substituents selected from: halogeno, amino, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, hydroxy, $C_{1-4}$alkoxy, $C_{1-4}$alkylsulphanyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonylamino, $C_{1-4}$alkanoyl, carboxy, phenyl, sulphate, phosphate and a group $-Y^3R^{28}$ (wherein $Y^3$ is $-NR^{29}C(O)-$ or $-O-C(O)-$ (wherein $R^{29}$ represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{28}$ is $C_{1-7}$alkyl, $C_{3-7}$cycloalkyl or a group $R^{30}$ wherein $R^{30}$ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, cyano, $-CONR^{31}R^{32}$ and $-NR^{31}COR^{32}$ (wherein $R^{31}$, $R^{32}$, $R^{33}$ and $R^{34}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl))), and

a group $-Y^4R^{35}$

(wherein $Y^4$ is $-C(O)-$, $-OC(O)-$, $-O-$, $-SO-$, $-SO_2-$, $-OSO_2-$, $-NR^{36}-$, $-NR^{37}C(O)-$, $-OC(O)O-$, $-C(O)NR^{38}-$ or $-NR^{39}C(O)O-$ (wherein $R^{36}$, $R^{37}$, $R^{38}$ and $R^{39}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{35}$ is a sugar moiety, a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, sulphate, $C_{1-7}$alkyl, $C_{1-7}$alkoxy, $C_{1-7}$alkanoyl, amino$C_{1-7}$alkylamino, $C_{1-7}$alkylamino$C_{1-7}$alkylamino, di($C_{1-7}$alkyl)amino$C_{1-7}$alkylamino, $C_{1-7}$alkylphosphate

(which alkyl, alkoxy, alkanoyl, aminoalkylamino, alkylaminoalkylamino, dialkylaminoalkylamino, or alkylphosphate may bear one or more substituents selected from:

halogeno, amino, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, hydroxy, $C_{1-4}$alkoxy, $C_{1-4}$alkylsulphanyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonylamino, $C_{1-4}$alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group $-Y^5R^{40}$ (wherein $Y^5$ is $-NR^{41}C(O)-$, $-C(O)NR^{42}-$, $-C(O)-O-$ or $-O-C(O)-$ (wherein $R^{41}$ and $R^{42}$ which may be the same or different each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{40}$ is $C_{1-7}$alkyl, $C_{3-7}$cycloalkyl, carboxy$C_{1-7}$alkyl or a group $R^{43}$ wherein $R^{43}$ is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, cyano, $-CONR^{44}R^{45}$ and $-NR^{46}COR^{47}$ (wherein $R^{44}$, $R^{45}$, $R^{46}$ and $R^{47}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl))),

$R^{48}$ (wherein $R^{48}$ is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$haloalkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, phenyl, cyano, $-CONR^{49}R^{50}$ and $-NR^{51}COR^{52}$ (wherein $R^{49}$, $R^{50}$, $R^{51}$ and $R^{52}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl)), or

$R^{53}$ (wherein $R^{53}$ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, $C_{1-4}$alkyl, $C_{1-4}$hydroxyalkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxy$C_{1-4}$alkyl, $C_{1-4}$alkylsulphonyl$C_{1-4}$alkyl and $R^{54}$ (wherein $R^{54}$ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, $C_{1-}$

$_4$alkyl, $C_{1-4}$hydroxyalkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxy$C_{1-4}$alkyl and $C_{1-4}$alkylsulphonyl$C_{1-4}$alkyl)));

with the proviso that $R^5$ is not hydroxy, alkoxy, substituted alkoxy, $-OPO_3H_2$, $-O-C_{1-7}$alkanoyl or benzyloxy;

with the further proviso that at least one of $R^5$ or $R^6$ is a group $-Y^4R^{35}$ (wherein $Y^4$ and $R^{35}$ are as defined hereinbefore) but with the further provisos

that when $R^5$ is $-Y^4R^{35}$ and $R^6$ is hydrogen, hydroxy or methoxy $-Y^4R^{35}$ is not selected from cases wherein:

$Y^4$ is -C(O)-, -OC(O)-, -O-, -SO-, $-OSO_2$-, $-NR^{36}$-, $-NR^{37}C(O)$- or $-C(O)NR^{38}$- (wherein $R^{36}$, $R^{37}$ and $R^{38}$, which may be the same or different, each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{35}$ is

a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, $C_{1-7}$alkyl, $C_{1-7}$alkoxy, $C_{1-7}$alkanoyl,

(which alkyl, alkoxy or alkanoyl may bear one or more substituents selected from: halogeno, hydroxy, and a group $-Y^5R^{40}$ (wherein $Y^5$ is -C(O)-O- or -O-C(O)- and $R^{40}$ is $C_{1-7}$alkyl)), or

$R^{48}$ (wherein $R^{48}$ is a phenyl group or a benzyl group which phenyl or benzyl group may bear one or more substituents selected from $C_{1-7}$alkyl); and

that when $R^6$ is $-Y^4R^{35}$ and $R^5$ is hydrogen, hydroxy or methoxy $-Y^4R^{35}$ is not selected from cases wherein:

$Y^4$ is -C(O)-, -O- or $-OSO_2$- and $R^{35}$ is

$C_{1-7}$alkyl, $C_{1-7}$alkoxy

(which alkyl, alkoxy or alkanoyl may bear one or more substituents selected from: halogeno),

$R^{48}$ (wherein $R^{48}$ is a benzyl group which phenyl or benzyl group may bear one or more substituents selected from $C_{1-7}$alkyl), or

$R^{53}$ (wherein $R^{53}$ is piperidinyl);

and salts thereof, pharmaceutically acceptable salts thereof, solvates and hydrates thereof, and prodrugs thereof for example esters, amides and sulphides.

In one embodiment of the invention preferred compounds include those in which $R^1$, $R^2$ and $R^3$ are each alkyl, $Y^4$ is NH and $R^{35}$ is an acyl group derived from a natural alpha-amino acid such as glycine, L-alanine or L-serine.

In one embodiment of the invention more preferred compounds include compounds wherein $R^1$, $R^2$ and $R^3$ are each methyl, $R^4$ is hydrogen and X is -CH(NHC(O)$CH_3$)-.

In another embodiment of the invention particular compounds include compounds wherein $R^1$, $R^2$ and $R^3$ are each alkyl and $R^{35}$ is amino$C_{1-7}$alkylamino, $C_{1-7}$alkylamino$C_{1-7}$alkylamino, di($C_{1-7}$alkyl)amino$C_{1-7}$alkylamino, 1-piperazinyl or 4-(piperidino)piperidin-1-yl.

In another embodiment of the invention further particular compounds include compounds wherein $R^1$, $R^2$ and $R^3$ are each alkyl, $R^4$ is hydrogen and X is -CH(NHC(O)$CH_3$)-.

In another embodiment of the invention more particular compounds include compounds wherein $R^1$, $R^2$ and $R^3$ are each alkyl and $R^4$ and $R^6$ are each hydrogen.

In another embodiment of the invention especially preferred compounds include compounds wherein $R^1$, $R^2$ and $R^3$ are each methyl and $R^{35}$ is a substituted acyl group.

Preferred compounds of the present invention include:

N-[3-(alanylamino)-9,10,11-trimethoxy-6,7-dihydro-5H-dibenzo[a,c]cyclohepten-5-yl]acetamide and salts thereof, pharmaceutically acceptable salts thereof, solvates and hydrates thereof, and prodrugs thereof for example esters, amides and sulphides.

A preferred compound for use in the manufacture of a medicament for use in the production of a vascular damaging effect in warm-blooded animals such as humans is *N*-[3-amino-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-yl]acetamide.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined' or 'defined hereinbefore', or 'hereinafter defined' or 'defined hereinafter', the said group encompasses the first occurring and broadest definition as well as each and all of the preferred definitions for that group.

In this specification unless stated otherwise the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. An analogous convention applies to other generic terms. Unless otherwise stated the term "alkyl" advantageously refers to chains with 1-7 carbon atoms, preferably 1-4 carbon atoms. The term "alkoxy" as used herein, unless stated otherwise includes "alkyl"-O- groups in which "alkyl" is as hereinbefore defined. The term "aryl" as used herein unless stated otherwise includes reference to a $C_{6-10}$ aryl group which may, if desired, carry one or more substituents selected from halogeno, alkyl, haloalkyl, alkoxy, hydroxy, amino, nitro and cyano, (wherein alkyl, haloalkyl and alkoxy are as hereinbefore and hereinafter defined). The term "aryloxy" as used herein unless otherwise

stated includes "aryl"-O-groups in which "aryl" is as hereinbefore defined. The term "sulphonyloxy" as used herein refers to alkylsulphonyloxy and arylsulphonyloxy groups in which "alkyl" and "aryl" are as hereinbefore defined. The term "alkanoyl" as used herein unless otherwise stated includes formyl and alkylC=O groups in which "alkyl" is as defined hereinbefore, for example $C_2$alkanoyl is ethanoyl and refers to $CH_3C=O$, $C_1$alkanoyl is formyl and refers to CHO. In this specification unless stated otherwise the term "alkenyl" includes both straight and branched chain alkenyl groups but references to individual alkenyl groups such as 2-butenyl are specific for the straight chain version only. Unless otherwise stated the term "alkenyl" advantageously refers to chains with 2-7 carbon atoms, preferably 2-4 carbon atoms. In this specification unless stated otherwise the term "alkynyl" includes both straight and branched chain alkynyl groups but references to individual alkynyl groups such as 2-butynyl are specific for the straight chain version only. Unless otherwise stated the term "alkynyl" advantageously refers to chains with 2-7 carbon atoms, preferably 2-4 carbon atoms. The term "halogeno" means fluoro, chloro, bromo or iodo unless otherwise stated. A haloalkyl group is an alkyl group as defined hereinbefore substituted with one or more halogeno groups for example trifluoromethyl and dichloromethyl.

An aromatic heterocyclic group includes those selected from pyridyl, pyrimidyl, furyl, thienyl, pyrrolyl, pyrazolyl, indolyl, benzofuryl, benzothienyl, benzothiazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, quinolyl and isoquinolyl.

For the avoidance of any doubt, it is to be understood that when $Y^1$ is, for example, a group of formula $-C(O)NR^{11}-$, it is the nitrogen atom bearing the $R^{11}$ group which is attached to the group $R^{10}$ and the carbonyl group (C(O)) is attached to the nitrogen atom which is linked to the hepten ring. A similar convention applies to the other two atom $Y^1$ linking groups such as $-SO_2NR^{12}-$. An analogous convention applies to other groups. It is further to be understood that when $Y^1$ represents $-C(O)NR^{11}-$ and $R^{11}$ is $C_{1-3}$alkoxy$C_{2-3}$alkyl it is the $C_{2-3}$alkyl moiety which is linked to the nitrogen atom of $Y^1$ and an analogous convention applies to other groups.

For the avoidance of any doubt it is to be understood that when $Y^2$ is, for example, a group of formula -OC(O)- it is the oxygen atom which is bound to the substituted group and the carbonyl group (C(O)) which is bound to $R^{13}$ and an analogous convention applies to other groups.

For the avoidance of any doubt it is to be understood that when $Y^4$ is, for example, a group of formula $-NR^{39}C(O)O-$ it is the nitrogen atom which is bound to the benz ring and the oxygen atom which is bound to $R^{35}$ and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when a group carries a $C_{1-4}$alkylamino substituent it is the amino moiety which is attached to the group whereas when a group carries a $C_{1-4}$aminoalkyl substituent it is the $C_{1-4}$alkyl moiety which is attached to the group and an analogous convention applies to other substituents.

Within the present invention it is to be understood that a compound of the formula I or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which has vascular damaging activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It will be appreciated that compounds of the formula I or a salt thereof may possess an asymmetric carbon atom. Such an asymmetric carbon atom is also involved in the tautomerism described above, and it is to be understood that the present invention encompasses any chiral form (including both pure enantiomers and racemic mixtures), as well as any tautomeric form, which has vascular damaging activity, and is not to be limited merely to any one tautomeric form or chiral form utilised within the formulae drawings. It is to be understood that the invention encompasses all optical and diastereomers which have vascular damaging activity.

It is also to be understood that certain compounds of the formula I and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which have vascular damaging activity.

The present invention relates to the compounds of formula I as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula I and their pharmaceutically acceptable salts. Pharmaceutically

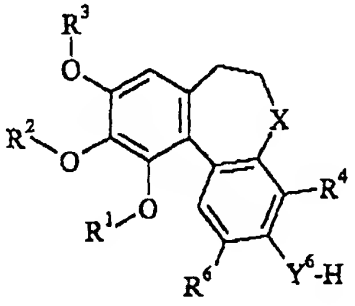
acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula I as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides (especially hydrochloric or hydrobromic acid of which hydrochloric acid is particularly preferred) or with sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. Suitable salts include hydrochlorides, hydrobromides, phosphates, sulphates, hydrogen sulphates, alkylsulphonates, arylsulphonates, acetates, benzoates, citrates, maleates, fumarates, succinates, lactates and tartrates. In addition where the compounds of formula I are sufficiently acidic, pharmaceutically acceptable salts may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium salt or for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Compounds of Formula I may be prepared by any process known to a person skilled in the art. Such processes include, for example, solid phase synthesis. Compounds of Formula I may be prepared by a number of processes as generally described hereinbelow and more specifically in the Examples hereinafter. In the general preparations described hereinafter it may be necessary to employ protecting groups which are then removed during the final stages of the synthesis. The appropriate use of such protecting groups and processes for their removal will be readily apparent to those skilled in the art. Processes for the preparation of novel compounds of formula I, are provided as a further feature of the invention and are as described hereinafter. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

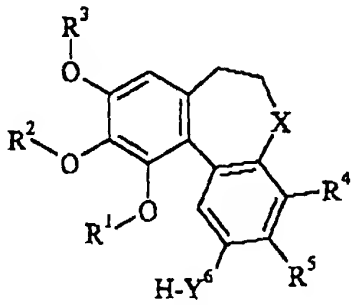
Thus, the following processes (a) to (h) and (i) to (iii) constitute further features of the present invention.

Synthesis of Compounds of Formula I

(a) Thus according to a further aspect of the invention a compound of formula I, in which $R^5$ or $R^6$ is a group $Y^4R^{35}$ (wherein $R^{35}$ is as defined hereinbefore and $Y^4$ is a group -OC(O)- or -NHC(O)-), can be prepared from a compound of formula III or IV:



(III)



(IV)

(wherein X, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$ are as defined hereinbefore and $Y^6$ is -O- or -NH-), as appropriate, by standard acylation or coupling conditions including, for example, treatment of a compound of formula III or IV with a substituted carboxylic acid in the presence of a coupling agent such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and, optionally, a base such as an organic base for example triethylamine in a solvent such as an aprotic solvent for example dimethylformamide or in a chlorinated solvent for example trichloromethane or dichloromethane at a temperature in the range from about -30°C to about 60°C, conveniently at or near ambient temperature.

(b) In another general example a compound of formula I, in which $R^3$ or $R^6$ is a group $Y^4R^{35}$ (wherein $R^{35}$ is $C_{1-7}$alkoxy which may be substituted as defined hereinbefore and $Y^4$ is a group -OC(O)- or -NHC(O)-), can be prepared from a compound of formula III and IV, as appropriate, by standard acylation reactions including, for example, treatment of a compound of formula III or IV with a substituted alkylchloroformate in the presence of a base such as an organic base for example, triethylamine or *N*-methylmorpholine in a solvent such as an ether solvent for example tetrahydrofuran or in a chlorinated solvent for example dichloromethane at a temperature in the range from about -20°C to the reflux temperature of the solvent.

(c) In a further general example a compound of formula I, in which $R^5$ or $R^6$ is a group $Y^4R^{35}$ (wherein $R^{35}$ is amino$C_{1-7}$alkylamino, $C_{1-7}$alkylamino$C_{1-7}$alkylamino, di($C_{1-7}$alkyl)amino$C_{1-7}$alkylamino and may be substituted as defined hereinbefore, or is $R^{53}$ (wherein $R^{53}$ is as defined hereinbefore) and $Y^4$ is a group -OC(O)- or -NHC(O)-), can be prepared from a compound of formula III or IV, as appropriate, by standard acylation reactions including, for

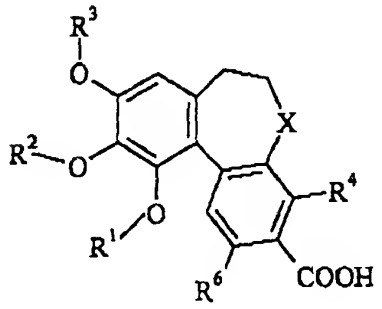
example, treatment of a compound of formula III or IV with a substituted alkylisocyanate or a carbamoyl chloride in the presence of a base such as an organic base for example triethylamine, pyridine or *N*-methylmorpholine in a solvent such as an ether solvent for example tetrahydrofuran or in a chlorinated solvent for example dichloromethane at a temperature in the range from about -20°C to the reflux temperature of the solvent.

(d) In a further example a compound of formula I, in which $R^5$ or $R^6$ is a group $Y^4R^{35}$ (wherein $R^{35}$ is a sugar moiety and $Y^4$ is a group -O- or -NH-), can be prepared from a compound of formula III or IV, as appropriate, by standard glycosylation reactions including for example treatment of a compound of formula III or IV with a suitably protected 1-bromo sugar in a solvent such as a chlorinated solvent for example trichloromethane or an aromatic solvent for example toluene at a temperature in the range from about 0°C to the reflux temperature of the solvent, followed by deprotection. Suitable protecting groups include acetyl groups for the sugar hydroxyl groups and esters for sugar carboxylic acids.

(e) In a further example a compound of formula I in which $R^5$ or $R^6$ is a group $Y^4R^{35}$ (wherein $R^{35}$ is sulphate and $Y^4$ is a group -O- or -NH-), can be prepared from a compound of formula III or IV, as appropriate, by standard sulphonylation reactions including for example treatment of a compound of formula III or IV with chlorosulphonic acid in the presence of a base such as dimethylaniline in a chlorinated solvent such as trichloromethane at a temperature in the range from about -20°C to about 60°C.

(f) In a further example a compound of formula I in which $R^5$ or $R^6$ is a group $Y^4R^{35}$ (wherein $R^{35}$ is $C_{1-7}$alkylphosphate and may be substituted as defined hereinbefore and $Y^4$ is a group -O- or -NH-), can be prepared from a compound of formula III or IV, as appropriate, by standard phosphorylation reactions including for example treatment of a compound of formula III or IV with phosphorus oxychloride in the presence of a base such as triethylamine in a chlorinated solvent such as trichloromethane at a temperature in the range from about -20°C to about 60°C, followed by treatment with an alcohol.

(g) Compounds of formula I in which $R^5$ is amino can be prepared from carboxylic acids of formula V:



(V)

(wherein X, $R^1$, $R^2$, $R^3$, $R^4$ and $R^6$ are as defined hereinbefore) via Curtius rearrangement and hydrolysis (V. Fernholz Justus Liebigs Ann., 1950, 568, 63-72).

(h) Compounds of formula I may also be prepared from other compounds of formula I by chemical modification. Examples of such chemical modifications that may be applied are standard alkylation, arylation, heteroarylation, acylation, thioacylation, sulphonylation, sulphation, phosphorylation, aromatic halogenation and coupling reactions. These reactions may be used to add new substituents or to modify existing substituents. Alternatively, existing substituents in compounds of formula I may be modified by, for example, oxidation, reduction, elimination, hydrolysis or other cleavage reaction to yield other compounds of formula I.

Thus for example a compound of formula I containing an amino group may be acylated on the amino group by treatment with, for example, an acyl halide or anhydride in the presence of a base, for example a tertiary amine base such as triethylamine, in for example, a solvent such as a hydrocarbon solvent e.g. dichloromethane at a temperature in the range for example -30°C to 120°C, conveniently at or near ambient temperature.

In another general example of an interconversion process an amino group in a compound of formula I may be sulphonylated by treatment with, for example, an alkyl or aryl sulphonyl chloride or an alkyl or aryl sulphonic anhydride in the presence of a base, for example a tertiary amine base such as triethylamine, in for example a solvent such as a hydrocarbon solvent e.g. dichloromethane at a temperature in the range for example -30°C to 120°C, conveniently at or near ambient temperature.

In a further general example a compound of formula I containing a hydroxy group can be converted into the corresponding dihydrogenphosphate ester by treatment with for example di-tert-butyl diisopropylphosphoramidite or di-tert-butyl diethylphosphoramidite in the

presence of a suitable catalyst for example tetrazole in a solvent such as an ether solvent for example tetrahydrofuran at a temperature in the range -40°C to 40°C, conveniently at or near ambient temperature, followed by treatment with an oxidising agent for example 3-chloroperoxy benzoic acid at a temperature in the range -78°C to 40°C preferably -40°C to 10°C. The resulting intermediate phosphate triester is treated with an acid for example trifluoroacetic acid in a solvent such as a chlorinated solvent e.g. dichloromethane at a temperature in the range -30°C to 40°C conveniently at or near 0°C to give the compound of formula I containing a dihydrogenphosphate ester.

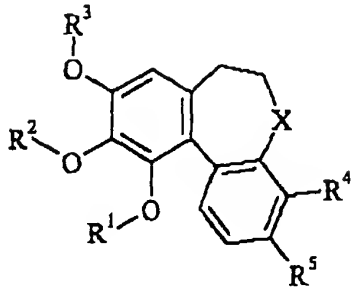
In a further general example a compound of formula I containing an amide can be hydrolysed by treatment with for example an acid such as hydrochloric acid in a solvent such as an alcohol, for example methanol at an elevated temperature conveniently at the reflux temperature.

In another general example an O-alkyl group may be cleaved to the corresponding alcohol (OH) by reaction with boron tribromide in a solvent such as a chlorinated solvent e.g. dichloromethane at a low temperature e.g. around -78°C.

In a further general example compounds of formula I may be alkylated by reaction with a suitable alkylating agent such as an alkyl halide, an alkyl toluenesulphonate, an alkyl methanesulphonate or an alkyl triflate. The alkylation reaction can be carried out in the presence of a base for example an inorganic base such as a carbonate e.g. caesium or potassium carbonate, a hydride such as sodium hydride or an alkoxide such as potassium t-butoxide in a suitable solvent such as an aprotic solvent e.g. dimethylformamide or an ether solvent such as tetrahydrofuran at a temperature of around -10°C to 80°C.

Synthesis of Intermediates

(i) Compounds of formula III or IV, used as starting materials for the preparation of compounds of the invention are either known or can be prepared from known compounds by the application of standard procedures of organic synthesis known in the art. For example a compound of formula VI:



(VI)

(wherein X, $R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are as defined hereinbefore), can be converted into a compound of formula IV where $Y^6$ is NH by the sequential application of standard nitration conditions followed by reduction of the incorporated nitro group under standard reduction conditions. Suitable nitration conditions include, for example, treatment with concentrated nitric acid in a solvent such as glacial acetic acid at a temperature from about -40°C to about 40°C. Suitable reduction conditions include, for example, treatment with tin(II) chloride in a solvent such as hydrochloric acid, with or without an alcoholic cosolvent, at a temperature between ambient temperature and about 100°C.

(ii) Compounds of formulae III or IV can also be prepared from other compounds of formulae III or IV by chemical modification. For example a compound of formula IV in which $Y^6$ is NH can be converted into the corresponding compound in which $Y^6$ is O by treatment with sodium nitrite in sulphuric acid at around 0°C followed by heating to around 100°C.

Preparation of a compound of formula I as a single enantiomer or, where appropriate, diastereomer may be effected by synthesis from an enantiomerically pure starting material or intermediate or by resolution of the final product in a conventional manner.

Acid addition salts of the compounds of formula I are prepared in a conventional manner by treating a solution or suspension of the free base I with about one equivalent of a pharmaceutically acceptable acid. Salts of compounds of formula I derived from inorganic or organic bases are prepared in a conventional manner by treating a solution or suspension of the free acid I with about one equivalent of a pharmaceutically acceptable organic or inorganic base. Alternatively both acid addition salts and salts derived from bases may be prepared by treatment of the parent compound with the appropriate ion-exchange resin in a standard fashion. Conventional concentration and recrystallistion techniques are employed in isolating the salts.

(iii) Compounds of formula V may be prepared from the corresponding colchicine derivatives by treatment with sodium methoxide in methanol followed by ester hydrolysis with aqueous acid or aqueous base (V. Fernholz Justus Liebigs Ann., 1950, 568, 63-72). Compounds of formula VI may be prepared by any of the methods described for compounds of formula I.

Many of the intermediates defined herein, for example, those of the formulae III, IV, V, and VI are novel and these are provided as a further feature of the invention. The preparation of these compounds is as described herein and/or is by methods well known to persons skilled in the art of organic chemistry.

Compounds according to the invention are able to destroy vasculature that has been newly formed such as tumour vasculature while leaving unaffected normal, mature vasculature. The identification of compounds which selectively, and preferably potently, damage newly-formed vasculature is desirable and is the subject of the present invention. The ability of the compounds to act in this way may be assessed, for example, using one or more of the procedures set out below:

(a) Activity against tumour vasculature measured by radioactive tracer

This assay demonstrates the ability of compounds to damage selectively tumour vasculature.

Subcutaneous CaNT tumours were initiated by injecting 0.05ml of a crude tumour cell suspension, approximately $10^6$ cells, under the skin overlying the rear dorsum of 12-16 week-old mice. The animals were selected for treatment after approximately 3-4 weeks, when their tumours reached a geometric mean diameter of 5.5-6.5 mm. Compounds were dissolved in sterile saline and injected intraperitoneally in a volume of 0.1 ml per 10g body weight. Tumour perfusion was measured 6 hours after intraperitoneal administration in tumour, kidney, liver, skin, muscle, gut and brain by the $^{86}$RbCl extraction technique (Sapirstein, Amer. Jnl. Physiol., 1958, 193, 161-168). Tissue radioactivity measured 1 minute after an intravenous injection of $^{86}$RbCl was used to calculate relative blood flow as a proportion of cardiac output (Hill and Denekamp, Brit. Jnl. Radiol., 1982, 55, 905-913). Five animals were used in control and treated groups. Results were expressed as a percentage of the blood flow in the corresponding tissues in vehicle treated animals.

(b) Activity against tumour vasculature measured by fluorescent dye

This assay demonstrates the ability of compounds to damage tumour vasculature.

Tumour functional vascular volume in CaNT tumour-bearing mice was measured using the fluorescent dye Hoechst 33342 according to the method of Smith et al (Brit. Jnl. Cancer 1988, 57, 247-253). Five animals were used in control and treated groups. The fluorescent dye was dissolved in saline at 6.25mg/ml and injected intravenously at 10mg/kg 24 hours after intraperitoneal drug treatment. One minute later, animals were killed and tumours excised and frozen; 10μm sections were cut at 3 different levels and observed under UV illumination using an Olympus microscope equipped with epifluorescence. Blood vessels were identified by their fluorescent outlines and vascular volume was quantified using a point scoring system based on that described by Chalkley, (Jnl. Natl. Cancer Inst., 1943, 4, 47-53). All estimates were based on counting a minimum of 100 fields from sections cut at the 3 different levels.

The ability of the compounds to bind to preparations of mammalian tubulin can be evaluated by a number of methods available in the literature, for example by following temperature initiated tubulin polymerisation by turbidity in the absence and presence of the compound (for example O.Boye *et al* Med. Chem. Res., 1991, 1, 142-150).

The activity of *N*-[3-amino-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-yl]acetamide, (V. Fernholz Justus Liebigs Ann., 1950, 568, 63-72), against tumour vasculature was measured by the fluorescent dye method described above. This compound decreased perfused vascular volume by 88% relative to control when dosed at 50mg/kg intraperitoneally. The $IC_{50}$ of this compound in a tubulin polymerisation assay was 58 micromolar (O.Boye *et al* Med. Chem. Res., 1991, 1, 142-150).

The activity of compounds Examples 2 and 3 (described hereinafter) against tumour vasculature was measured by the fluorescent dye method described hereinbefore.

| Compound of Example | % Decrease in vascular volume |
|---|---|
| 2 | 95 |
| 3 | 45 |

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula I as defined hereinbefore or a

pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for nasal administration or administration by inhalation, for example as a powder or solution, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) for example as a sterile solution, suspension or emulsion, for topical administration for example as an ointment or cream or for rectal administration for example as a suppository. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compositions of the present invention are advantageously presented in unit dosage form. The compound will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000mg per square metre body area of the animal, i.e. approximately 0.1-100mg/kg. A unit dose in the range, for example, 1-100mg/kg, preferably 1-50mg/kg is envisaged and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250mg of active ingredient.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 1-50mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a compound of the formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

A further feature of the present invention is a compound of formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament, conveniently a compound of formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament for producing a vascular damaging effect in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof in the manufacture

of a medicament for use in the production of a vascular damaging effect in a warm-blooded animal such as a human being.

According to a further feature of the invention there is provided a method for producing a vascular damaging effect in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore.

The antiangiogenic treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the antiangiogenic treatment defined hereinbefore may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may include the following categories of therapeutic agent:

(i) other antiangiogenic agents that work by different mechanisms from those defined hereinbefore (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function, angiostatin, endostatin, razoxin, thalidomide);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen,toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrazole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide), inhibitors of testosterone $5\alpha$-dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors);

(iii) biological response modifiers (for example interferon);

(iv) antibodies (for example edrecolomab); and

(v) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); enzymes (for example asparaginase); thymidylate synthase inhibitors (for example raltitrexed); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, irinotecan).

As stated above the compounds defined in the present invention are of interest for their vascular damaging effects. Such compounds of the invention are expected to be useful in the prophylaxis and treatment of a wide range of disease states where inappropriate angiogenesis occurs including cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin.

In addition to their use in therapeutic medicine, the compounds of formula I and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of in vitro and in vivo test systems for the evaluation of the effects of vascular damaging agents in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

It is to be understood that where the term "ether" is used anywhere in this specification it refers to diethyl ether.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

(iii) yields are given for illustration only and are not necessarily the maximum attainable;

(iv) the structures of the end-products of the formula I were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(v) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

**Example 1**

*N*-[3-((*N*-benzyloxycarbonylalanyl)amino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-yl]acetamide

A solution of *N*-benzyloxycarbonyl-(L)-alanine (63mg, 0.28mmol) in dichloromethane (4ml) at -20°C was treated with *N*-[3-amino-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohpeten-5yl]acetamide (100mg, 0.28mmol), (V. Fernholz Justus Liebigs Ann., 1950, 568, 63-72), and 1,3-dicyclohexylcarbodiimide (134mg, 0.31mmol) and the solution stirred for 16 hours at ambient temperature. Solvent was evaporated under reduced pressure and the residue chromatographed on silica gel, eluting with ethyl acetate to give a white solid which was triturated with diethyl ether. The title compound (85mg) was obtained as a white solid.

m.p. 140-141°C

m/e 561

**Example 2**

*N*-[3-(alanylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-yl]acetamide

A solution of *N*-[3-((*N*-benzyloxycarbonylalanyl)amino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-yl]acetamide (70mg, 0.125mmol), (prepared as

described in Example 1), in ethanol (2ml) was hydrogenated at atmospheric pressure over 5% palladium on carbon (10mg) for 2 hours. Ethanol (3ml) was added and the solution was filtered through diatomaceous earth and the filtrate concentrated under reduced pressure. Trituration with ethyl acetate/diethyl ether gave the title compound (35mg) as a white solid.

m.p. 170-173°C

m/e 427

**Example 3**

*N*-[3-(4-(1-piperidinyl)piperidinylcarbonyloxy)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5yl]acetamide

A solution of *N*-acetyl-colchinol (300mg, 0.84mmol), (J. Cech F. Santacy Collect. Czech Comm 1949, 4, 532-539), in pyridine (5ml) was treated with 4-piperidinopiperidine carbamoyl chloride (346mg, 1.5mmol), (K.H.Henegar J.Org. Chem., 1997, 62, 6588-6597) and the solution heated at reflux for 1 hour. The cooled mixture was filtered and the filtrate concentrated under reduced pressure. The residue was purified on silica gel eluting with methanol to give the title compound (180mg) as a white solid.

m.p. 168-175°C

m/e 551